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**REMARKS**

**Status of the Claims**

In ¶1 of the Office Action, the Examiner acknowledged the receipt and confirmed the entry of the Preliminary Amendment submitted June 25, 2001 wherein claims 1-39 were cancelled without prejudice or disclaimer and new claims 40-47 were introduced. Thus, claims 40-47 are pending in the present application.

**Rejection Under 35 U.S.C. §112, Second Paragraph**

The Examiner stated in ¶3 of the Office Action that claims 40-47 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner stated that the claims recite various binding characteristics vis-à-vis the antibodies of interest which are vague and indefinite. The Examiner stated that these characteristics are ambiguous because the results will vary depending upon the HIV-1 envelope employed. The Examiner stated that, for instance, the PA-3 Mab displays inhibitory rates of 85% and 90% when the HIV-1 envelopes from isolates JR-FL and LAI are respectively employed. Thus, the Examiner stated that absent further defining criteria, the skilled artisan cannot accurately ascertain the metes and bounds of the claimed invention. The Examiner stated that applicants should amend the claim language to clearly and

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unambiguously set forth the binding characteristics of the antibodies employed in the inhibitory method.

In response, applicants respectfully traverse the Examiner's rejection for the reasons which follow.

In essence, the Examiner's position is that the binding characteristics recited in the claims, vis-à-vis the antibodies of interest, are ambiguous because the results (i.e., the percentage of fusion inhibition) will vary depending upon which strain of HIV-1 is employed (JR-FL or LAI) and that this ambiguity renders the claims vague and indefinite. The second paragraph of 35 U.S.C. §112 requires that the claims "particularly point out" and "distinctly claim" that which the applicant regards as his invention. Since, as discussed below, applicants' claims (e.g., claim 40) particularly and distinctly identify (1) the target cell line employed; (2) the HIV-1 envelope employed; and (3) the resultant ranges of fusion inhibition achieved, without any ambiguity, applicants submit that the subject claims meet all of the requirements of 112, second paragraph, and are thus neither vague nor indefinite.

As demonstrated, for example, in Table 1 on page 34 of the specification, there are several factors which affect the degree of fusion inhibition achieved with the novel monoclonal antibodies recited for use in the claimed method of the invention. One of these factors is, as noted by the Examiner, the HIV-1 envelope which is employed (e.g., JR-FL or LAI). Another such factor is the CD4+ target cell line

which is chosen. For example, as set forth in Table 1, HIV-1<sub>LAI</sub> envelope glycoprotein-mediated membrane fusion with PM-1 cells was inhibited 89.7% by the PA-3 antibody, whereas the use of a different CD4+ cell line, e.g., SUP-T1 cells, produced only 2.5% inhibition. A third factor involves the particular antibody chosen, including but not limited to PA-3, PA-5, PA-6 and PA-7.

Thus the claims have been written to take into account the varying effects attributable to the use of (1) various HIV-1 envelopes, (2) a variety of CD4+ target cell lines, and (3) a variety of monoclonal antibodies, all of which are identified in the claims with particularity and specificity. In particular, independent claim 40 takes into account the differing effects attributable to the above-mentioned variants by reciting a method of inhibiting HIV-1 infection of a CD4+ cell which comprises contacting the CD4+ cell with an amount of a monoclonal antibody or portion thereof effective to, *inter alia*:

- specifically inhibit 67% or greater of fusion of a CD4+ PM-1 cell to a HeLa cell expressing envelope glycoprotein from HIV-1<sub>JR-FL</sub>; and
- inhibit 18% or less of fusion of a CD4+ SUP-T1 cell to a HeLa cell expressing envelope protein from HIV-1<sub>LAI</sub>.

The claim therefore recites a range of fusion inhibition values (i.e., "greater than 67%" and "less than 18%") which

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can vary (within these claimed ranges) according to the choice of (1) the HIV-1 envelope; (2) the target CD4+ cell line, and (3) the particular antibody or fragment thereof contacted with the CD4+ cell. As the fusion inhibition values recited in claim 40 are all completely supported by the experimental data provided in Table 1 and discussed at pp. 33-34 of the specification, applicants submit that the subject claim meets all of the requirements of 35 U.S.C. §112 and is thus neither vague nor indefinite. Moreover, claims 41-47 all depend, directly or indirectly on claim 40. Thus these claims incorporate all of the recitations of the subject claim and they too are believed to meet all of the requirements of §112. The Examiner is therefore respectfully requested to reconsider and withdraw his rejection of claims 40-47 under §112, ¶2.

**Rejections Under 35 U.S.C. §112, First Paragraph**

In ¶5 of the Office Action, the Examiner stated that claims 40-47 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, citing *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981) and *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). The Examiner stated that the claims include the limitations "specifically inhibit 67% or greater" and "inhibit 18% or less of fusion" which fail to receive adequate support in the disclosure. The Examiner stated that the disclosure

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describes the preparation, isolation, and preliminary characterization of four monoclonal antibodies produced by the hybridomas designated PA-3, -5, -6, and -7. The Examiner stated that applicants initially attempted to identify HIV-1 fusion inhibitory antibodies that did not bind specifically to CD4. The Examiner stated that immunization strategies employing HeLa and C8166 cell lines, as well as proteinase-digested human erythrocytes, were initially employed. The Examiner stated that, however, these strategies all failed to produce antibodies with the desired characteristics. The Examiner stated that finally, PM-1 cells were employed as an immunogen and four hybridoma cell lines were identified that produced antibodies with the desired characteristics (i.e., HIV-1 fusion inhibitory without binding to CD4 or the viral env). The Examiner stated that preliminary characterization of these antibodies suggests that PA-3 and PA-5 recognize CD11a or CD18, whereas PA-6 and PA-7 recognize HLA Class II. The Examiner stated that the fusion inhibitory activities of these antibodies were further characterized in HeLa-env RET assay wherein it was reported that PA-3, -5, -6, and -7 inhibited fusion between PM-1 cells and HeLa-env<sub>JR-FL</sub> 85%, 96%, 92% and 67%, respectively. The Examiner stated that fusion inhibitory studies involving HeLa-env<sub>LAI</sub> cell lines provided inhibitory values of 90%, 100%, 81% and 69% for said antibodies. The Examiner stated that Sup-T1 fusion inhibitory studies produced inhibitory rates of 2.5%, 0%, 18%, and 11%. Thus, the Examiner stated that the skilled artisan would reasonably conclude that applicants were in possession of the monoclonal antibodies PA-3, -5, -

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6, and -7. The Examiner stated that appropriate inhibitory methodology claim language employing these four Mabs would be acceptable.

The Examiner stated that applicants are reminded that the essence of the statutory requirement governing written description is whether one skilled in the art, familiar with the practice of the art at the time of the filing date, could reasonably have found the later claimed invention in the specification as filed, citing *In re Kaslow*, 707 F. 2d 1366, 1375, 217 U.S.P.Q. 1089, 1096 (Fed. Cir. 1983), *In re Wilder*, 736 F.2d 1516, 1520 222 U.S.P.Q. 349,372 (Fed. Cir. 1984, cert. denied, 469 U.S. 1209 (1985)), and *Texas Instruments, Inc. v. International Trade Comm'n*, 871 F.2d 1054, 1063, 10 U.S.P.Q.2d 1257, 1263 (Fed. Cir. 1989). The Examiner stated that moreover, the courts have stated that the evaluation of written description is highly fact-specific, and that broadly articulated rules are inappropriate, citing *In re Wertheim*, 541 F.2d 257, 263, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976) and *In re Driscoll*, 562 F.2d 1245, 1250, 195 U.S.P.Q. 434, 438 (C.C.P.A. 1977). The Examiner stated that it is also important to remember that the true issue in question is not whether the specification enables one of ordinary skill in the art to make the later claimed invention, but whether or not the disclosure is sufficiently clear that those skilled in the art will conclude that the applicant made the invention having the specific claim limitations, citing *Martin v. Mayer*, 823 F.2d 500, 505, 3 U.S.P.Q.2d 1333, 1337 (Fed. Cir. 1987).

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The Examiner stated that upon perusal of the disclosure, the skilled artisan would not conclude that applicants were in possession of monoclonal antibodies with the currently claimed binding characteristics. The Examiner stated that the claims are currently directed toward a large genus of antibodies that were neither contemplated nor described by the applicants. The Examiner stated that while a small number of antibodies have been identified and partially characterized, at no time did applicants contemplate making and using antibodies with the specifically recited binding characteristics. The Examiner stated that there is no description of attempting to isolate and purify antibodies with specific inhibitory ranges of 67% or greater in PM-1 cell lines or 18% or less in Sup-T1 cell lines. The Examiner stated that thus, the claimed ranges are not supported by the disclosure. The Examiner stated that the courts have also concluded that the disclosure of a single or limited number of species is insufficient support for claims directed toward a broader genus, citing *In re Gosteli*, 872 F.2d 1008, 1010, 10 U.S.P.Q.2d 1614, 1616 (Fed. Cir. 1989), *In re Blaser*, 556 F. 2d 534, 538-39, 194 U.S.P.Q. 122, 125-26 (C.C.P.A. 1977), *In re Wertheim*, 541 F.2d 257, 263, 191 U.S.P.Q. 90,97 (C.C.P.A. 1976) and *In re Lukach*, 442 F.2d 967, 969, 169 U.S.P.Q. 795, 797 (C.C.P.A. 1971). The Examiner stated that thus, the skilled artisan would reasonably conclude that applicants were not in possession of the claimed invention at the time of filing.

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The Examiner then additionally stated in ¶6 of the Office Action that claims 40-47 are further rejected under U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, again citing *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981) and *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). The Examiner stated that to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention, citing to *Vas-Cath, Inc., v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q. at 1116.

The Examiner stated that the issue raised in this application is whether the original application provides adequate support for fusion inhibitory methods employing the broadly claimed genus of monoclonal antibodies. The Examiner stated that an applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention, citing *Lockwood v. American Airlines, Inc.* 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). The Examiner stated that the claimed invention as a whole may not be adequately described where an invention is described solely in terms



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of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. The Examiner stated that a biomolecule sequence described only by functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest, citing *In re Bell*, 991 F.2d 781, 26 U.S.P.Q. 2d 1529 (Fed. Cir. 1993) and *In re Deuel*, 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995). The Examiner stated that a lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process, citing to *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1995). The Examiner stated that the court noted in this decision that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not reasonably lead those skilled in the art to any particular species.

The Examiner stated that an applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. The Examiner stated that an applicant may also show that an invention is complete by disclosure of

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sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. The Examiner stated that for some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight. The Examiner stated that the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. The Examiner stated that without such a correlation, the capability to recognize or understand the structure from the mere recitation of function and minimal structure is highly unlikely. The Examiner stated that in the latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement, citing to *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 U.S.P.Q.2d 1398, 1404, 1406 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998) and *In re Wilder*, 736 F.2d 1516, 1521, 222 U.S.P.Q. 369, 372-3 (Fed. Cir. 1984). The Examiner stated that factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled

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with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

The Examiner stated that in the instant application, the disclosure provides generic methods for obtaining antibodies that are capable of inhibiting HIV-1 envelope-mediated cell fusion. However, the Examiner stated that these screening procedures are not designed to identify Mabs with the currently claimed binding characteristics. The Examiner stated that they are simply designed to identify fusion inhibitors. Moreover, the Examiner stated that the disclosure fails to provide any detailed guidance pertaining to the structural characteristics of the monoclonal antibodies employed in the fusion assay. The Examiner stated that applicants have failed to provide any guidance pertaining to the amino acid sequence of any of the given antibodies. The Examiner stated that applicants have failed to provide any detailed structural guidance pertaining to the antigenic determinants that are recognized by said antibodies. Thus, the Examiner stated that the disclosure fails to provide even a modicum of structural information pertaining to the antibodies of interest. Moreover, the Examiner stated that the disclosure does not provide a reproducible method of making antibodies with the claimed binding characteristics. The Examiner stated that four antibodies were identified using the claimed method and they all had different binding characteristics. The Examiner stated that these findings are not unexpected given the unpredictability of the art. Accordingly, the Examiner stated that the skilled artisan

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would reasonably conclude that applicants have failed to provide an adequate written description for the claimed genus of antibodies employed in the claimed methodology.

In response, applicants respectfully traverse the Examiner's above rejections. Applicants contend that one skilled in the art, familiar with the practice of the art at the time of the filing date, could reasonably have found the invention as now claimed in the specification as filed. The disclosure is sufficiently clear that those skilled in the art would readily conclude that applicants made the invention having the limitations recited in applicants' present claims. Thus the original application provides adequate support for fusion inhibitory methods employing the claimed genus of monoclonal antibodies.

As of the effective filing date of this application, i.e., January 17, 1996, one skilled in the art would have been able to make an antibody such as those recited in applicants' claims (see, e.g., claim 40) for use in the presently claimed method. In support, applicants attach hereto as **Exhibit A** a Declaration Under 37 C.F.R. §1.132 of Ronald C. Kennedy ("Kennedy declaration" or simply, "declaration").

As pointed out, for example, in ¶ 7 of the Kennedy declaration, it was standard practice as of January 17, 1996 for one skilled in this art to make a monoclonal antibody by immunizing a mouse with a particular immunogen. Moreover, monoclonal technology, according to the

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declarant, is a technology that was widely used and highly predictable as of January 17, 1996.

Dr. Kennedy states further, at ¶9 of his declaration, that based on the disclosure contained in applicants' specification, coupled with the general knowledge in the field about making monoclonal antibodies as of January 17, 1996, one skilled in the art could have readily made a monoclonal antibody such as that recited for use in the claimed method. Further according to Dr. Kennedy, making monoclonal antibodies to cell surface markers on whole cells was a well-defined technology as of January 17, 1996. As of January 17, 1996, the level of skill of one of ordinary skill in the art of making a monoclonal antibody was a laboratory technician with a bachelor's degree and one to two years of experience working with hybridomas. Such a person of ordinary skill could have readily made a monoclonal antibody such as is recited in the claims for use in applicants' claimed method prior to January 17, 1996. In particular, the experimental details section of the application's specification teaches on pages 24-36 a straightforward, reproducible method for making and identifying such a monoclonal antibody.

Further to the above, the application provides detailed guidance and direction for making a monoclonal antibody and selecting a monoclonal antibody having the desired characteristics as recited in applicants' claims. As pointed out, for example, in ¶¶10-14 of the Kennedy

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declaration, the application describes, among other things, the following:

- a) a source of an immunogen for eliciting a monoclonal antibody for use in the method of the invention (PM-1 cells, page 33, lines 9-11);
- b) a method for obtaining a monoclonal antibody by recovering supernatant from hybridomas generated by immunizing mice with PM-1 cells (page 24);
- c) a screening assay called the resonance energy transfer ("RET") assay for identifying a monoclonal antibody having the ability to inhibit HIV-1 envelope glycoprotein mediated membrane fusion (pages 25-26);
- d) adaptations to the RET screening assay such that HeLa cells expressing envelope glycoprotein from HIV-1<sub>JR-FL</sub> ("HeLa-env<sub>JR-FL</sub> cells") and HeLa cells expressing envelope glycoprotein from HIV-1<sub>LAI</sub> ("HeLa-env<sub>LAI</sub> cells") may be used for differential screening (page 25) for monoclonal antibodies having the characteristics as recited in the claims for antibodies which will function in accordance with the method recited in applicants' claims.
- e) Monoclonal antibodies generated by immunizing mice with CD4+ PM-1 cells which inhibit fusion between HeLa-env<sub>JR-FL</sub> and CD4+ PM-1 cells; the identification and selection of monoclonal antibodies that fit the characteristics of inhibiting fusion between CD4+ PM-1 cells and HeLa-env<sub>JR-FL</sub> cells by at least 67% and only inhibiting fusion between CD4+SUP-T1 cells

and HeLa-env<sub>LAI</sub> cells by at most 18% (Table 1 on page 34).

- f) Additional methods are provided for further characterization of the fusion-inhibiting monoclonal antibodies for use with the method of the present invention. These methods, which are described at pages 26-30 and 34-34 of applicants' specification, demonstrated that the fusion-inhibiting monoclonal antibodies for use in the claimed method react with an antigen on the surface of a PM-1 cell, do not react with HIV-1 envelope glycoprotein or CD4, and do not cross-react with an antigen on the surface of a SUP-T1 cell.
- g) The application describes specific examples of monoclonal antibodies made using the above-described methodology which are useful in the method of the invention in Table 1 on page 34.

As additionally pointed out in ¶11 of the Kennedy declaration, it is not necessary for one of ordinary skill in the art to know the antigenic determinants or epitopes on the whole cells used for immunization, or their structural configuration in order to make and successfully identify a monoclonal antibody having the fusion-inhibition characteristics required to practice the method of the invention. Further according to the declarant, it is well-established that having a starting immunogenic source such as an immunogenic whole cell and following an immunization method, a series of monoclonal antibodies will be elicited and that the screening method taught in the application

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allows one skilled in the art to identify and select monoclonal antibodies which, in accordance with the claimed method, when contacted with a CD4+ cell, will (a) specifically inhibit 67% or greater of fusion of a CD4+ PM-1 cell to a HeLa cell expressing envelope glycoprotein from HIV-1<sub>JR-FL</sub>, and (b) inhibits 18% or less of fusion of a CD4+ SUP-T1 cell to a HeLa cell expressing envelope protein from HIV-1<sub>LAI</sub>, wherein the antibody (i) does not cross-react with HIV-1 envelope glycoprotein or CD4, (ii) reacts with an antigen on the surface of a PM-1 cell, and (iii) does not react with an antigen on the surface of a SUP-T1 cell, so as to thereby inhibit HIV-1 infection of the CD4+ cell.

Dr. Kennedy additionally pointed out, in ¶12 of his declaration, that various immunogenic whole cells, such as PM-1 cells, HeLa cells, C8166 cells and protease digested human erythrocytes, were used to generate monoclonal antibodies. One of the immunogenic whole cells, i.e., PM-1 cells, resulted in eliciting antibodies that blocked fusion of CD4+ PM-1 cells to HeLa-env<sub>JR-FL</sub> cells, as identified by the screening methods. Thus the specification unequivocally shows that PM-1 cells or analogous cells may be successfully used as an immunogen to make an HIV-1 fusion-blocking antibody as disclosed in the specification for use in the method recited in the claims.

Accordingly, therefore, applicants respectfully submit that one skilled in this art, familiar with the practice of the art at the time of the filing date, would reasonably have found, in the specification as filed, a teaching of how to



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make, select and characterize monoclonal antibodies as recited in claims 40-47. As demonstrated above, applicants' disclosure is sufficiently clear that one of ordinary skill in this art would have concluded that applicants were in possession of monoclonal antibodies having the currently claimed binding characteristics and that the application thus provides adequate support for fusion inhibitory methods employing the presently claimed monoclonal antibodies. Applicants contend, therefore, that the remarks provided above, as supported by the declaration of Dr. Kennedy, which is entitled to evidentiary weight under 37 C.F.R. §1.132, are sufficient to obviate the above rejection under §112, ¶1 and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

#### Summary

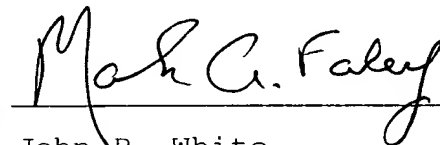
For the reasons provided above, the Examiner is respectfully requested to reconsider and withdraw the grounds for rejection of the claims and earnestly solicit allowance of the now pending claims, i.e., nos. 40-47.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants attorneys invite the Examiner to telephone either of them at the number provided below.

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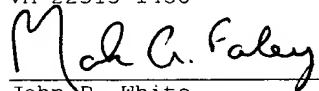
No fee, except a \$465.00 fee for a three month extension of time for filing a three month extension of time is believed to be due. A check in the amount of \$465.00 is therefore enclosed herewith. Should any additional fee(s) be due in regard to this application, authorization is hereby provided to charge the required amount to Deposit Account No. 03-3125.

Respectfully submitted,



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